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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,318	01/19/2000	Lola M. Reid	113918.101	3032

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	22

DATE MAILED: 07/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/487,318	REID ET AL.	
	Examin r	Art Unit	
	Quang Nguyen, Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

THE REPLY FILED 18 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *18 June 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See Continuation Sheet*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-6,8,9,11-35,38,39 and 42-48*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

DAVID GUZO
PRIMARY EXAMINER

Continuation of 2. NOTE: Claim 38 in the proposed amendment is dependent on the canc lled claim 21. This will rais a new ground of rejection. Additionally, the scope of the n wly amended claim 12 is no longer the same as th scope of the finally rejected claim 12 because the mixture of cells in step (c) is now comprised of an enriched population of human hepatic progenitors, rather than an enriched population of human liver liver progenitors which comprise h patic progenitors, hemopoeitic progenitors, mesenchymal prog nitors or combinations thereof. This will raise n w issu s that require further consideration and/or search as well as potential n w grounds of rejections (e.g., arts or 112, Second paragraph for dependent claims).

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' arguments are found unpersuasive fo the reasons discussed below.

(1) With respect to the rejections over Muench et al. under 35 U.S.C. 102(b) for claims 21-23 and 42-44 which would have been cancelled if the present Amendment has been entered, Applicants argue that the hemopoietic progenitor cells of the Muench referenc s are distinct and different from hepatic progenitor cells of the present invention because hepatic progenitors are defined in the present application as cells that give rise to hepatocytes and biliary cells, including three subpopulations: hepatic stem cells, committed hepatic progenitors, and committed biliary progenitors, and that hepatic stem cells as separate and distinct from hemopoietic stem cells. Additionally, Applicants argue that the claimed human hepatic pluripotent progenitors do not share all of the same common cell surfac antigens with the human fetal liver hemopoietic progenitor cell populations of the Muench references. For example, whereas the Muench references disclose cells that are CD38- and CD14-, Applicants' hepatic progenitor cells express a CD14+, CD38+ phenotype.

Please note that the claims are drawn to human hepatic pluripotent progenitors, and that human hepatic pluripotent progenitors comprise hepatic progenitors, hemopoietic progenitors, mesenchymal progenitors or combinations thereof as clearly indicated by claim 22 which is dependent upon claim 21. Additionally, the claimed human hepatic pluripotent progenitors are not required to expr ss CD14+ and CD38+ markers, but rather any one of the following markers CD14, CD34, CD38, CD117, ICAM or combinations thereof. Therefore, the human hepatic pluripotent progenitors as claimed are indistinguishable over the isolated human fetal liver progenitor cell populations of Muench et al.

(2) With respect to the rejection over Craig et al. under 35 U.S.C. 102(b) for claims 1-2, 4-6, 8-9, 11-14, 18-23 and 42-44, Applicants argue that hemopoietic progenitor cells as described by Craig are distinct and different from hepatic progenitor cells of the present invention. The claimed human hepatic pluripotent progenitors do not share the same expression of cell surface antigens with the human liver hemopoietic progenitor cell populations of Craig. Whereas the Craig reference discloses cells that are CD38 low, CD45RO+, CD117low, the instant hepatic progenitor cells express a CD38+, CD45-, CD117+ phenotype as disclosed and claimed. Applicants further argue that Craig's method selects against the hepatic progenitor cells claimed by Applicants for two main reasons. Firstly, Craig selects for Thy-1 expression in every case and that Craig teaches that Thy-1 staining was highest on CD38-CD34+ cells, and decreas d with increased CD38 expression, whereas Applicants' claimed hepatic progenitors express CD38 in all cases, and strongly or very strongly in some cases. Secondly, Craig is disclosing that CD45 expression is fundamental to the types of cells Craig's method is intended to isolate, hemopoeitic progenitor cells, whereas the instant specification recites "cells exhibiting CD45, which is expressed on all mature hemopoietic cells" are removed via immunoselection if selection of hepatic progenitors of the present invention is intended".

Please note that the claims recite human liver progenitors not hepatic progenitors, and according to the instant specification human liver progenitors are defined as a cell population from liver, including hepatic progenitors, hemopoietic progenitors and mesenchymal progenitors (page 22, lines 9-10). Clearly, the human liver progenitors of the present invention includes human liver hemopoietic progenitors. Furthermore, as noted above human hepatic pluripotent progenitors of the present invention comprise hepatic progenitors, hemopoietic progenitors, mesenchymal progenitors or combinations thereof, and not solely a homologous population of human hepatic progenitor cells. Furthermore, what is the difference between cells expressing CD38low and/or CD117low and cells expressing CD38+ and/or CD117+? The + merely indicates a positive expression for the markers CD38 and/or CD117, and not any degree (e.g., strong or strongly xpression) of marker expression. Therefore, the Craig reference still anticipates the instant claims.

(3) With respect to the rejection over Faris under 35 U.S.C. 102(e) for claims 11, 20, 21-26 and 42-44 which would have been canc lled if the present Amendment has been entered, Applicants simply state that the rejection is mooted because of the cancellation of the claims. The rejection is still maintained for the reasons of record.

(4) With respect to the rejection over Reid (U.S. 6,069,005) in view of Mikata and Naughton under 35 U.S.C. 103(a) for claims 1-6, 8, 12-19 and 45-48, Applicants mainly argue that Reid teaches away from the use of a low centrifugation step by citing the following paragraphs, "methods for isolation of hepatoblasts require the use of fractionation methods for cell size or cell density which are inadequate for separating the hemopoeitic from the hepatopoietic precursors" (col. 4, lines 12-15), "The advantage of this protocol in comparison with previous methods which involved attachment of dispersed liver cells to culture dishes, low-speed differential centrigugation, and culture in argine-deficient medium are several fold" (col. 19, lines 19-40). Applicants further argue using a centrifugation st p of Mitaka, the h patoblasts in the Reid's method would b thrown away becaus dissociated fetal h patoblasts also readily form large aggregates and that these large aggregat s would be found in the discarded pellet fraction. Additionally, Applicants argue that one skilled in the art would have little motivation to add a low-speed centrifugation to the method of Reid as Reid teaches that such a step is unn c ssary.

Please note that the present invention is drawn to a composition as well as a method for prepare the same, wherein the composition comprises a mixture of cells derived from human liver tissue containing an enriched population of human liver progenitors comprising hepatic progenitors, hemopoietic progenitors, mesenchymal progenitors or combinations thereof. Since it is not necessary to separate the hemopoietic precursors/progenitors from the hepatopoitic precursors/progenitors, and instead the presence of hemopoietic progenitors is desirable in the composition together with the hepatopoietic progenitors, the use of a low speed centrifugation step is in effect a desirable step (a motivation), and therefore the teachings of Reid do not teach away but rather provide support for the modified method as stated in the Final Office rejection. Additionally, the low centrifugation step of Mitaka would not result in the throw away of large aggregated hepatoblasts due to the ability of dissociated fetal hepatoblasts to form readily large aggregates. This is because Reid specifically teaches that the tendency of the cells to aggregate is prevented by maintaining the cells at 4C and by removing calcium with EGTA interfering with CAM-mediated aggregation (col. 19, lines 41-43). Furthermore, as stated in the previous Final Office action, on of ordinary skilled artisan would also have been motivated to further introduce a low speed centrifugation in the modified isolation procedure to remove the bulk of large mature hepatocytes or parenchymal cell from progenitor cell populations (5-15 microns in diameter), so that less contaminating large sized parenchymal cells (or aggregates) are present in the cell suspension subjected to panning and fluorescence activated cell sorting procedures because Reid clearly teaches that FACS (Fluorescence activated cell sorting) procedure demands a single cell suspension (col. 19, lines 48-49).

(5) With respect to the rejection over the Muench references in view of Reid (U.S 5,789,246) for claims 21 and 38, Applicants argu mainly the the Muench references taken alone or together or in combination with Reid fail to teach or suggest the cells or cell population of the present invention.

Please note that the claims are drawn to human hepatic pluripotent progenitors, and that human hepatic pluripotent progenitors comprise hepatic progenitors, hemopoietic progenitors, mesenchymal progenitors or combinations thereof as clearly indicated by claim 22 which is dependent upon claim 21. Additionally, the claimed human hepatic pluripotent progenitors are not required to express CD14+ and CD38+ markers, but rather any one of the following markers CD14, CD34, CD38, CD117, ICAM or combinations thereof. Therefore, the human hepatic pluripotent progenitors as claimed are indistinguishable over the isolated human fetal liver progenitor cell populations of Muench et al.

(6) With respect to the rejection under 35 U.S.C. 112 First Paragraph for claims 27-35 and 39 which would have been cancelled if the present Amendment has been entered, Applicants simply traverse the rejection. The rejection is maintained for the reasons of record.